Declining Semen Quality and Increasing Incidence of Testicular Cancer: Is There a Common Cause?

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Male reproduction has been given little attention in science and in medical practice. However, a recent metaanalysis on semen quality, which clearly pointed to a decrease over the past 50 years, has been repeatedly quoted. Three recent reports have found that semen quality has declined among candidate semen donors during the past 20 years. The evidence of decline in the quality of semen is not the only indicator that the human testis is at risk. During the past 50 years, cancer of the testis has also become more common. This is a disorder of young men, and it is associated with a high rate of other abnormalities of the testis including undescended testis and poor semen quality. Furthermore, the incidence of both hypospadias and undescended testis has been reported to be rising in the general population. We believe that the evidence of declining semen quality should be seen in the light of these trends in other reproductive disorders of men. However, the etiology is unknown. A recent hypothesis that links the trends in the health of the male reproductive system to xenoestrogens in the environment is discussed. — Environ Health Perspect 103(Suppl 7):137–139(1995)

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Introduction

There is a growing concern that abnormalities often associated with testicular cancer are becoming more frequent; this is evidenced by an increasing incidence of testicular cancer (*1–4*) during the past decades, as well as a possible increase in the occurrence of cryptorchidism (*5,6*) and hypospadias (*7*). Furthermore, these changes have been accompanied by a significant decline in semen quality (*8–10*). The causes of the increasing incidence of abnormalities in male reproductive function are not known. However, it has been suggested that there may be an etiological association. In addition, due to the increased frequency of reproductive abnormalities, it seems most probable that they reflect adverse effects of environmental or lifestyle factors rather than genetic changes. A hypothesis has been forwarded that these changes in male reproductive function may be caused by the impact of an increasing environmental burden of estrogens (*11*).

Testicular cancer develops from a noninvasive stage of carcinoma *in situ* (CIS). CIS cells have characteristics of malignant primordial gonocytes. Therefore, testicular cancer is believed to arise from fetal germ cells (*12*). Reliable data indicate that there has been a marked time-related increase in the incidence of this neoplasm. Thus, the Danish Cancer Registry has recorded a 3- to 4-fold increase in the frequence of testicular germ cell cancer from the 1940s to the 1980s (*1*). Denmark is a high risk area for testicular cancer. Similar increments have been reported in countries with a lower incidence, i.e., the United States (*2*) and Scotland (*4*). Even in countries with a low incidence of testicular cancer (i.e., Finland), an increase has been noted during the past decades (*3*).

Cryptorchidism and hypospadias are genitourinary abnormalities that arise during fetal development. Increased incidence of these abnormalities has recently been reported; Chilvers et al. (*5*) reported an apparent doubling of the frequency of undescended testes from the 1950s to the 1970s. Similar results have been obtained in other studies (*6*). Although the data on hypospadias may be less convincing, they seem to confirm that there has been an increasing incidence (*13*).

A number of studies over the past 10 to 20 years have suggested that sperm counts in men have declined; however, little notice has been paid to these reports, possibly because they were based on selected groups of men (*8*). A systematic review of the international literature on semen analysis performed in normal men, including almost 15,000 men in 61 publications revealed a highly significant drop in mean sperm counts from 113 million/ml in 1940 to 66 million/ml in 1990 (*8*) (Figure 1). In addition, it appeared that the number of men with oligozoospermia (< 20 million/ml) and sperm counts in the lower end of the normal range (20–40 million/ml) had increased, whereas the percentage of those with high sperm counts (> 100 million/ml) (*8*) has decreased. Thus, the population of men with poor semen quality had increased. These changes in sperm counts may have a negative influence on male fertility.

Clinical experience indicates that there might be an etiological association among all the previously mentioned abnormalities of male reproductive function. Testicular cancer and cryptorchidism, as well as hypospadias, are often associated with a

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Abbreviations used: CIS, carcinoma *in situ*; FSH, follicule-stimulating hormone; MIS, Müllerian-inhibiting substance; SHBG, sex hormone-binding globulin.

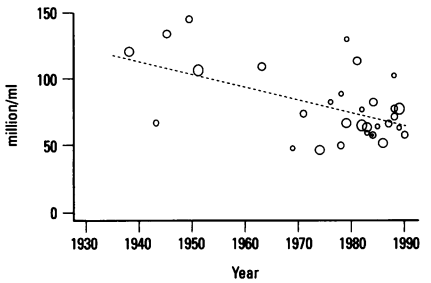

Figure 1. Linear regression of mean sperm density reported in 61 publications (represented by circles whose area is proportional to the logarithm of the number of subjects in study), each weighted according to number of subjects, 1938 to 1990. Data from Carlsen et al. (*8*).

histological pattern of impaired spermatogenesis (*13,14*). In addition, it is well known that testicular cancer arises more often in maldescended testes (*14*), and infertile men may have an increased risk of testicular cancer.

Recently, it has been hypothesized that male reproductive abnormalities may be due to an increased level of maternal estrogens affecting the developing fetus (*11*). The basis for the susceptibility to adverse effects of estrogens focuses on the effects of this hormone on development and function of Sertoli cells of the fetal testis (*15*). The proliferation and function of Sertoli cells are controlled by the pituitary hormone follicle-stimulating hormone (FSH) (*15*), which in turn is under negative feedback regulation by estrogens (*15*). FSH stimulates multiplication of Sertoli cells and probably also regulates the secretion of Müllerian-inhibiting substance (MIS) (*16*), which is responsible for regression of Müllerian ducts (*17*). Decrease in FSH secretion from fetal pituitary—due to elevated maternal estrogen levels—may have an inverse effect on Sertoli-cell proliferation and secretion of MIS. It has also been suggested that impaired secretion of MIS might lead to different types of intersex conditions and cryptorchidism because MIS may also play a role in the abdominal phase of testicular descent (*17*). Furthermore, there seems to be evidence that MIS controls division of early germ cells; insufficient MIS production might cause abnormal proliferation of germ cells; and thereby plays a role in development of CIS germ cells, which give rise to testicular cancer in adult life (*18*).

Multiplication of Sertoli cells is largely restricted to fetal and early neonatal life (*15,19*) and is controlled by the production of FSH. Each Sertoli cell can support only a finite number of germ cells to develop into mature spermatozoa. A low number of Sertoli cells could therefore be a limiting factor in spermatogenesis.

Abnormal Sertoli-cell function may also have a negative impact on Leydig cells and consequently on the androgen production and the virilization of the fetus.

The physiological basis for a possible role of estrogens in male reproductive dysfunction seems to be feasible. Since the levels of maternal estrogens rise significantly during pregnancy as a physiological phenomenon, can an increase in maternal estrogen levels have such a profound effect on fetal genital organs? It should be kept in mind that the critical events of testicular development take place at the very early stages of fetal life, in a period that precedes the marked physiological increase in maternal estrogens. Increase in the basal levels of estrogens at this very early period of development may, therefore, have a deleterious effect on development of male reproductive organs. Furthermore, endogenous estrogens are normally bound to sex hormone-binding globulin (SHBG) with high affinity whereas synthetic estrogens are not (*20*); therefore, synthetic estrogens may have a profound biological effect, even when present in low concentration.

Experience with the synthetic estrogen diethylstilbestrol (DES) speaks in favor of the "estrogen hypothesis." Between 1950 and 1970, several million pregnant women were treated with DES, which led to substantial increases in the incidence of cryptorchidism and hypospadias in the male offspring, as well as decreased sperm counts and probably also increased incidence of testicular cancer in later life (*21*). Animal data also seem to support the hypothesis.

Evidence for increasing levels of estrogens during the past half century comes from several sources (*11,22*). Probably most important have been the overall change in diet and the increasing use of environmental chemicals, many of which are weak estrogens (*23,24*).

Although it seems likely that estrogens may play an important role in the development of male reproductive abnormalities, it should be remembered that the estrogen hypothesis (*11*) remains to be tested. It is hoped that the growing awareness that male reproductive function may be at risk will stimulate both basic and clinical research within this field that have received relatively little attention in the past.

REFERENCES

1. Prener A, Østerlind A. Cancer in Denmark. Copenhagen: Danish Cancer Registry, 1985.
2. Pottern LM, Brown LM, Hoover RN, Javadpour N, O'Connell KJ, Stutzman RE, Blattner WA. Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. J Natl Cancer Inst 74:377–381 (1985).
3. Hakulinen T, Andersen A, Malker B, Pukkala E, Schou G, Tulinius H. Trends in cancer incidence in the Nordic countries. Acta Pathol Microbiol Immunol Scand Suppl 288:1–151 (1986).
4. Boyle P, Kaye SB, Robertson AG. Changes in testicular cancer in Scotland. Eur J Cancer Clin Oncol 23:827–830 (1987).
5. Chilvers C, Pike MC, Forman D, Fogelman K, Wadsworth MEJ. Apparent doubling of frequency of undescended testis in England and Wales in 1962–81. Lancet 2(8398):330–332 (1984).
6. Jackson MB. The epidemiology of cryptorchidism. John Radcliffe Hospital Cryptorchidism Research Group. Horm Res 30:153–156 (1988).
7. Källén B, Bertollini R, Castilla E, Czeizel A, Knudsen LB, Martinez-Frias ML, Mastroiacovo P, Mutchinick O. A joint international study on the epidemiology of hypospadias. Acta Paediatr Scand Suppl 324:5–52 (1986).
8. Carlsen E, Giwercman A, Keiding N, Skakkebæk NE. Evidence for decreasing quality of semen during past 50 years. Br Med J 305:609–613 (1992).
9. Auger J, Czyglik F, Kunstmann JM, Jouannet P. Significant decrease of semen characteristics of fertile men from Paris area during the last 20 years [abstract]. Hum Reprod 9(Suppl 4):72 (1994).
10. Van Waeleghem K, De Clercq N, Vermeulen L, Schoonjans F, Comhaire F. Deterioration of sperm quality in young Belgian men during recent decades [abstract]. Hum Reprod 9(Suppl 4):73 (1994).

11. Sharpe RM, Skakkebæk NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 341:1392–1395 (1993).
12. Skakkebæk NE, Berthelsen JG, Giwercman A, Müller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. Int J Androl 10:19–28 (1987).
13. Källén B, Castilla EE, Kringelbach M, Lancaster PAL, Martinez-Frias ML, Mastroiacovo P, Mutchinick O, Robert E. Parental fertility and infant hypospadias: an international case-control study. Teratology 44:629–634 (1991).
14. Giwercman A, Bruun E, Frimodt-Møller C, Skakkebæk NE. Prevalence of carcinoma *in situ* and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol 142:998–1002 (1989).
15. Sharpe RM. Falling sperm counts in men—is there an endocrine cause? J Endocrinol 137:357–360 (1993).
16. Kuroda T, Lee MM, Haqq CM, Powell DM, Manganaro TF, Donahoe PK. Mullerian inhibiting substance ontogeny and its modulation by follicle-stimulating hormone in the rat testes. Endocrinology 127:1825–1832 (1990).
17. Hutson JM, Metcalfe SA, MacLaughlin DT, Cate RL, Cigarroa F, Ueno S, Donahoe PK. Müllerian inhibiting substance. In: The Testis. 2nd ed (Burger H, de Kretser DM, eds). New York:Raven Press, 1989;143–180.
18. Hirobe S, He W-W, Lee MM, Donahoe PK. Müllerian inhibiting substance messenger ribonucleic acid expression in granulosa and Sertoli cells coincides with their mitotic activity. Endocrinology 131:854–862 (1992).
19. Cortes D, Müller J, Skakkebæk NE. Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. Int J Androl 10:589–596 (1987).
20. Sheehan DM, Young M. Diethylstilbestrol and estradiol binding to serum albumin and pregnancy plasma of rat and human. Endocrinology 104:1442–1446 (1979).
21. Stillman RJ. *In utero* exposure to diethylstilbestrol: adverse effects on the reproductive tract and reproductive performance in male and female offspring. Am J Obstet Gynecol 142:905–921 (1982).
22. McLachlan JA. Functional toxicology: a new approach to detect biologically active xenobiotics. Environ Health Perspect 101:386–387 (1993).
23. Field B, Selub M, Hughes CL. Reproductive effects of environmental agents. Semin Reprod Endocrinol 8:44–54 (1990).
24. Colborn T, Clement C. Chemically-induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton, NJ:Princeton Scientific Publishing, 1992.